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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/734,472	12/12/2003	Marc F. Charette	JJJ-P02-510	9598

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EXAMINER	
WANG, CHANG YU	
ART UNIT	**PAPER NUMBER**
1649	

DATE MAILED: 11/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/734,472	CHARETTE, MARC F.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-32 and 34-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-32 and 34-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/12/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RESPONSE TO AMENDMENT

Status of Application/Amendments/claims

Applicant's amendment filed August 21, 2006 is acknowledged. Claims 1-26 and 33 are cancelled. Claims 27-32, 34-38 and newly added claims 39-50 are pending in this application and under examination. The text of those sections of Title 35, U.S. Code, not included in this action can be found in the previous office action.

Priority

This application repeats a substantial portion of prior Application No. 09/012846, filed Jan 24, 1998, and adds and claims additional disclosure not presented in the prior application. Since this application names an inventor or inventors named in the prior application, it may constitute a continuation-in-part of the prior application. Should applicant desire to obtain the benefit of the filing date of the prior application, attention is directed to 35 U.S.C. 120 and 37 CFR 1.78.

Applicant argues that amended claim 34 reciting residue 293-431 of SEQ ID NO:2, which corresponds to the mature form of OP-1, was described in the originally-filed specification because US 5266683 as referenced in the original specification describes the range of residues 293-431 corresponding to the mature form of OP-1. Applicant argues that the range of residues 30-431 of SEQ ID NO:2 as recited in claim 35 is supported by the original specification because

the osteogenic proteins having a N-terminal signal peptide sequence less than about 30 residues and if less than 30 residues are removed from OP-1 would result the protein comprising residues 30-431 of SEQ ID NO:2. In addition, Applicant argues that a morphogen comprising both a mature form (293-431) and a pro-form (30-292) of OP-1 would comprises residues 30-431 as recited in claim 35.

Applicant's arguments have been fully considered but they are not found persuasive. In response to Applicant's argument that US 5266683 ('683) supports the mature form of OP-1 as encompassing residues 293-431 of SEQ ID NO:2, it is noted that several possible mature forms of OP-1 that contain the active domain of OP-1 are described in '683 (see col. 8-9, Table I). Although Applicant describes the useful form of the protein including the mature form of OP-1, Applicant fails to specify which specific form would be useful in the claimed method as filed in the original specification since there are many possible mature forms of OP-1 described in '683. In response to Applicant's argument that a deletion less than 30 residues of the signal peptide would result in the protein comprising residues 30-431 of SEQ ID NO:2 as recited in claim 35, it is noted that the length of a general signal peptide is vary and the range could be from 8-30 amino acids based on the prediction of signal peptide sequence. Applicant argues that the instant application describing a protein without the signal peptide by a deletion of residues 1-29 of SEQ ID NO:2 would support the protein comprising residues 30-431 of SEQ ID NO:2 as recited in claim 35. It is not found persuasive because the instant application fails to teach that the mature form of

OP-1, as originally filed, encompasses a deletion missing exactly residues 1-29 of SEQ ID NO:2 and only consists of residues 30-431 of SEQ ID NO:2. In addition, '683 describes that the signal peptide for OP-1 is amino acids 26-30 at the N-terminus of OP-1. Thus, it is not clear which site of the signal peptide sequence would be cleaved in order to generate a mature form of OP-1, as described in the originally filed application.

For the reasons given above, the morphogens comprising residues 293-431 or 30-431 of SEQ ID NO:2 as recited in the claims 34-35 are not supported by the application No. 09/012846, filed Jan 23,1998, and thus considered as new matters. The instant specification only discloses a morphogen comprising residues 330-431, 30-292, or 48-292 of SEQ ID NO:2." (see p.12 in the specification). Therefore, the priority for the subject matter to the extent of residues 293-431 and 30-431 of SEQ ID NO:2 is Dec, 12, 2003.

Information Disclosure Statement

Applicant argues that all references listed in IDS can been found in the parent application 09/012846. However, the references lined-through cannot been found in 09/012846. Thus, the lined-through references listed in the IDS filed February 12, 2004 have not been considered.

Oath/Declaration

The requirement of a new oath/declaration is maintained. The instant application presents a claim for subject matter not originally claimed or embraced

in the statement of the invention. The specification only discloses a morphogen comprising residues 30-292, 330-431, or 48-292 of SEQ ID NO:2.

Specification

The objection to the specification as introducing new matter into the disclosure is maintained for reasons set forth above.

Claim Rejections/Objections Withdrawn

The rejection of claims 27-35 under 35 U.S.C. 102 (b) as being anticipated by Withers et al. (Society for Neuroscience Abstracts, (1997) Vol. 23, No. 1-2, pp. 1433.) is withdrawn in response to Applicant's argument.

Claim Rejections/Objections Maintained

The rejection of claims 27-38 under 35 U.S.C. 112, first paragraph because the specification is not enabling the invention commensurate in scope with the claims is maintained for reasons of record in the previous office action. The rejection is also applied to new claims 39-50.

Applicant argues that the rejection based on the premise that the effects of OP-1 on hippocampal neurites in vitro cannot be extrapolated to the effects in vivo is false because the prophetic examples 1-14 described in the specification provide enough guidance to enable one of skill in the art to practice the claimed invention. In addition, Applicant argues that the office action acknowledges a prophetic example enabling because example 18 in US 6723698 is a prophetic

example and has been cited to anticipate the instant claims. Applicant argues that the reference of Charron et al. is not related to the rejection because the examiner fails to provide any evidence that Shh is required for practicing the claimed invention. Further, Applicant argues that the examples shown in the reference contradict the role of gradients of Shh and BMP having a function in treating a damaged tissue and for synapse formation because OP-1 induces dendrite formation in cultured hippocampal neurons without the presence of Shh and any gradient of OP-1. Applicant further argues that even if OP-1 gradients were required for dendritic growth, the specification teaches the morphogen intraventricularly administered into the brain would be expected to from a gradient.

Applicant's arguments have been fully considered but they are not persuasive. In response to Applicant's arguments that the rejection based on in vitro data that cannot be extrapolated to the in vivo is wrong and the prophetic examples are enabling, it is noted that different diseases have different causes and the in vitro condition is optimized for neuronal survival. Based on the disclosure and prior art, Applicant is enabled for a method of enhancing synaptogenesis for neuronal survival in the hippocampus in vivo by administration of OP-1 to a subject. However, Applicant is not enabled for a method of reducing memory dysfunction associated with damaged hippocampal tissue because the memory function is complex and involved in more than neural survival and dendritic development. It requires reconnecting the damaged neurons and reestablishing synaptic plasticity and cognitive function of the brain.

Applicant fails to demonstrate that administration of OP-1 or related fragments as recited in the claims to a patient or animal suffering from memory dysfunction associated with damaged hippocampal tissue can enhance reconnecting the damaged neurons and reestablishing synaptic plasticity and cognitive function of the brain, which are required for reducing memory dysfunction. Thus, it is unpredictable whether OP-1 promotes synaptogenesis in the hippocampus in vivo can reduce memory dysfunction associated with damaged hippocampal tissue.

In response to Applicant's argument that the reference of Charron is not related to the rejection and the examiner fails to provide evidence that Shh and gradient of OP-1 are required for the claimed invention, the examiner asserts that the reference of Charron is related to the rejection. Charron et al teach that different concentrations of morphogens have different gradient effects on axonal guidance and subsequently affect synapse formation. For example, Sonic hedgehog (Shh) needs to coordinate with BMP in cell fate determination and axon guidance during neural development. Shh functions as a chemoattratant and BMP7:GDF7 heterodimers mediate a chemorepellent activity to collapse growth cone in the developing spinal cord, indicating that axonal guidance and synapse formation require a balance of concentration of different morphogens. However, Applicant fails to provide sufficient guidance as to enable one of skill in the art on how to use a morphogen with limited homology to OP-1 and related fragments as recited in claims 27-35 and 49 in reducing memory dysfunction in vivo caused by different mechanisms as recited in claims 39-42, 45-50. A

balance of concentration of different morphogens, such as a balance between Shh and BMP, is important for regulating synapse connection between axons and dendrites in the developing spinal cord, indicating that a balanced concentration of different morphogens is also important for synapse formation and synaptic plasticity in neural development in the hippocampus. However, Applicant fails to provide sufficient guidance as to how to achieve a balance of different morphogens in enhancing synapse formation and establishing synaptic plasticity in damaged hippocampal tissue in vivo and subsequently reducing memory dysfunction. In addition, OP-1 intraventricularly administered to the brain simply diffuses to different brain regions. It is unpredictable whether intraventricular administration of OP-1 at any concentration in the brain would achieve a balance of different morphogens that can enhance synapse formation and establishing synaptic plasticity that are required for reducing memory dysfunction. Therefore, in view of the necessity of experimentation, the limited working examples, the unpredictability of the art, and the lack of sufficient guidance in the specification, it would require more undue experimentation to practice the claimed invention as it pertains to a method for reducing memory dysfunction associated with damaged hippocampal tissue. Thus, the rejection of claims 27-38 under 35 U.S.C. §112, first paragraph, because the specification is not enabling the invention commensurate in scope with the claims is maintained. The rejection is also applied to new claims 39-50. Further, the Wands factors have been considered and those relevant to enablement of the instant invention are discussed.)

Claim Rejections - 35 USC § 102

The rejection of claims 27-38 under 35 U.S.C. 102 (e) as being anticipated by U. S. Patent No. 6723698 (Rueger et al. issued on April 20, 2004, effective filling date September 25, 1997) is maintained for reasons of record in the previous office action. the rejection is also applied to claims 39-46, 48-50.

Applicant argues that US 6723698 fails to teach all the features of the pending claims because examples 16.2,17 only relate to the effects of OP-1 on the dendrite arbor development but fail to teach administration of a morphogen to a mammal in reducing memory dysfunction. Applicant further argues that example 18 in '698 only teaches administration of a morphogen to a mammal but fails to teach the mammal having hippocampal damage and memory dysfunction and other disorders. Applicant further argues that even if '698 taught all the elements of claim 27, it fails to teach several dependent claims.

Applicant's arguments have been fully considered but they are not found persuasive. The method steps as recited in the claims are anticipated by the '698 patent; the claimed result, were it to occur, would simply be an inherent consequence of the method of the '698 patent. '698 anticipates the administration of OP-1 to a mammal in vivo to enhance synaptogenesis and neuronal survival in the hippocampus as recited in the procedures of the claimed method. In addition, the dependent claims recite using a morphogen comprising different fragments of SEQ ID NO:2/OP-1. In addition, '698 teaches an intraventricular administration route as in claim 43 (see col. 20, lines 20-25) and biocompatible microspheres to deliver the OP-1 as in claim 44 (see col. 21, lines

5-25). '698 also teaches administration of OP-1 to prevent neuronal cell death caused by ischemia (col.36 example 11), traumatic brain injury (col. 53, example 20), mechanical/chemical trauma/neurotoxin including ethanol (see col. 30, example 6), malnutrition, metabolic disorders (col.1, lines 42-50) as recited in claims 39-46, 48-50. Thus, the rejection is also applied to claims 39-46, 48-50.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 34 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claim as amended is directed to a method for reducing memory dysfunction associated with damaged hippocampal tissue in a mammal comprising administering a morphogen comprising residues 293-431 of SEQ ID NO:2. The instant claim now recites limitation of residues 293-431 of SEQ ID NO:2, which was not clearly disclosed in the specification and claim as filed, and now change the scope of the instant disclosure as filed. Such limitations recited

in the present claims, which did not appear in the specification or original claims, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant fails to disclose a morphogen comprising residues 293-431 of SEQ ID NO:2 as recited in claim 34. The specification fails to disclose the limitation. Applicant only discloses 30-292, 330-431, and 48-292 of SEQ ID NO:2 in the specification (p.12) and residues 292-431 of SEQ ID NO: 2 in claim 34. Accordingly, in the absence of sufficient recitation of time frame, the specification does not provide adequate written description to support the morphogen comprising residues 293-431 of SEQ ID NO:2 as recited in claim 34. Support is not found for the morphogen comprising residues 293-431 of SEQ ID NO:2 as disclosed in the original specification and thus the recitations constitute new matter absent evidence for their support. Applicant is required to cancel the new matter in the reply to this office action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 27-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6723698 (Rueger et al. issued on April 20, 2004, effective filling date September 25, 1997) in view of Kern et al. (Neurotoxicity. 1993. 14: 319-27)

U. S. Patent No. 6723698 ('698) teaches a morphogen comprising at least 70% homology with C-terminal seven cysteine skeleton of human OP-1 residues 330-431 of SEQ ID NO:2 and a morphogen containing sequences greater 60% identity to the conserved C-terminal seven-cysteine motif including residues 330-431 of OP-1 can enhance dendritic development and synaptogenesis and useful for potential treatment of several neurological disorders (column 13, lines 1-19). OP-1 enhances dendritic development and branches in hippocampal neurons in vitro. Cultured hippocampal neurons treated OP-1 have a dramatic increase of dendritic length and branches (see column 45, example 16, morphogen induce dendritic growth in various neurons:16.2 hippocampal neurons). In addition, OP-1 induces synaptogenesis in cultured hippocampal neurons vitro detected by MAP2 and synapsin antibodies (see column 50, example

17). '698 also teaches OP-1 induces synapstogenesis in hippocampal tissues in vivo (see column 50, example 18). '698 also teaches a method of improving motor function in mammals with symptoms of neural pathway damage in the peripheral nervous system and treating amyotrophic lateral sclerosis comprising administering the mammal with a morphogen comprising at least 70% homology with C-terminal seven cysteine skeleton of human OP-1 residues 330-431 of SEQ ID NO:2 or a morphogen containing sequences greater 60% identity to the conserved C-terminal seven-cysteine motif including residues 330-431 of OP-1 (see columns 69-72, claims 1-16). '698 further teaches morphogens for treatment selected from human OP-1, mouse OP-1, human OP-2, human OP-2, mouse OP-2, 60A, GDF-1, BMP2A, BMP2B, DPP, Vg1, Vgr-1, BMP3, BMP5 or BMP6. The sequence of OP-1 disclosed in '698 comprises the residues 30-292, 330-431, 48-292, 292-330, 292-431, and 30-431 of SEQ ID NO:2, which meets the limitations recited in the claims. Further, the sequences containing the residues 330-431 also anticipate the sequences containing the residues 292-431 or 30-431 of OP-1 (instant SEQ ID NO:2). '698 teaches intraventricular administration as in claim 43 (see col. 20, lines 20-25) and biocompatible microspheres as in claim44 (see col. 21, lines 5-25). '698 also teaches administration of OP-1 to prevent neuronal cell death caused by ischemia as in claims 40-41 (col.36 example 11), traumatic brain injury as in claim 42 (col. 53, example 20), mechanical/chemical trauma/ neurotoxin including ethanol as in claims 39,

45-46, 49 and 50 (see col. 30, example 6), malnutrition, metabolic disorders as in claims 48 (col.1, lines 42-50). But '698 fails to teach lead as a neurotoxin as in claim 47.

Kern et al. teach that lead has devastating effects on the developing nervous system and causes cognitive and behavior defects (see p. 319, abstract). Kern et al. teach that lead have neurotoxic effects on neurons and inhibits neurite development in cultured hippocampal and motor neurons (see p. 319, abstract).

It would have been obvious for one of ordinary skill in the art at the time of the instant invention was made to also prevent neuronal damage due to the toxicity of lead by administration of OP-1 since lead has been shown to cause neurotoxic effects on hippocampal neurons and OP-1 has been shown to be neuroprotective on neuronal damage caused by chemical/physical trauma/neurotoxin. The person of ordinary skill in the art would have been motivated to adminster OP-1 to the damaged hippocampus caused by neurotoxin such as lead because OP-1 has been shown to enhance neuronal survival and synapse development in the hippocampus. One of ordinary skill in the art would have expected success in reducing the neurotoxicity caused by lead by using OP-1.

Conclusion

NO CLAIM IS ALLOWED.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang, Ph.D. whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday and every other Friday from 8:30 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CYW
October 24, 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER